

Case report

Two subsequent metachroneous solid tumors: Oncocytic variant adrenocortical carcinoma and rhabdomyosarcoma of childhood: Case report and Literature Review

Short title: Two subsequent metachroneous solid tumors

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What is already known on this topic?

Adrenocortical carcinoma can be related to other cancer.

What does this study add?

Sequence analysis should be done if the FISH analysis is negative. Hounsfield Unit (HU) can provide benefit at the difference of malign from benign. Lin-Weiss-Bisceglia (LWB) system should be used instead of the Weiss system for the oncocytic variant.

Abstract

Most cases of malignancies appear to be sporadic, but some syndromes are associated with malignancies with germline variants. Herein, a child with an unusual association of oncocytic variant adrenocortical carcinoma (ACC) and rhabdomyosarcoma was presented.

An 18-month-old-boy was admitted with virilization of the genital area, penis enlargement, and erection which had begun six months ago. Serum total testosterone: 457 ng/dl (<10), androstenedione: 3.35ng/ml (<0.5) and DHEA-SO₄: 206 mcg/dl (<35) were measured higher than normal ranges. Right adrenal mass was detected. After adrenalectomy, histopathological examination revealed oncocytic variant ACC. Three-month later from surgery, the child then presented with 6x8 cm sized swelling of the left leg. Histopathological examination revealed embryonal RMS. Testing for tumour protein (TP53) variant by DNA sequence analysis was positive; however; FISH analysis was negative. After chemotherapy and local radiotherapy, the patient is in good condition without tumour recurrence. Only about one-third of these tumours have a variant of TP53. This status also applies to other genetic variants related to cancer. However, a significant association of malignancies strongly suggests a problem in tumour suppressor genes or new variants. Another suppressor gene that is yet unidentified can also be present and effective in this locus. The occurrence of ACC as a part of a syndrome and positive family history of malignancies in patients are clinically important. These patients and their families should be scanned for genetic abnormalities. The patient with ACC should be followed-up carefully for other tumours to detect malignancy early.

Key Words: Child, adrenocortical carcinoma, oncocytic variant, rhabdomyosarcoma, TP53

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Introduction

Oncocytic variant Adrenocortical carcinoma (ACC) is an extremely rare tumour, with an incidence of 0.72 per million populations annually (1, 2). In our country, ACCs account for

6.9 of carcinomas and other malignant epithelial tumours, and 0.19% of childhood cancers (3). Only 147 cases with adrenal oncocytic neoplasm have been reported in the literature (4). Although most cases of ACCs are sporadic, ACCs have an association with hereditary cancer syndromes such as Li-Fraumeni, Beckwith-Wiedemann (5). The pathogenesis of sporadic ACCs is less well understood. Tumour suppressor genes have a significant role in the development of cancer (6). Breast cancer, soft tissue and bone sarcoma, brain tumours, Wilms' tumour, neuroblastoma, hepatoblastoma are some types of cancer that are associated with ACCs. However, well-known oncogenes/tumour suppressor variants are not relevant to each malignancy. Environmental factors and decreased penetrance of a particular gene defect cannot be excluded (6).

In this report, we described clinical features of oncocytic variant adrenocortical carcinoma presenting as peripheral precocious puberty, and embryonal rhabdomyosarcoma developed as second malignancy. Moreover, we aimed to discuss the genetic variant.

Case report

An 18-month-old-boy was admitted at the department of pediatric endocrinology with virilization of the genital area, penis enlargement, and erection which had begun six months ago. Informed consent from the parents of the patients was obtained. Any information and features were not found in his personal and family history. There is not any consanguinity.

Anthropometric evaluation

Height:86 cm (P78),weight: 14.5 kg (P95), chronological/ height ages: 1.61/1.88 years old,height SDS/target height/target height SDS:+0.80/ 165 cm/-1.65. The gap between height SDS and target height SDS could be explained by accelerated growth velocity. Although the patient has phallic enlargement and pubarche for six months, his testicular size was consistent with the prepubertal period with 2 ml/2 ml. Hemihypertrophy was not detected.

Laboratory evaluation

Biochemical and complete blood count tests were within normal limits. His bone age was advanced and compatible with 3 years. Serum FSH:0.3 IU/L (0.3-4.6), LH: 0.12 IU/L (0.1-6), 17-OH progesterone: 0.5 ng/ml (0.1-0.9), T4: 0.96 ng/dl (0.81-1.73), TSH: 2.84 microIU/ml (0.8-6.26), ACTH: 21.7 pg/ml (0-46), cortisol: 10.7 microgr/dl (4.3-22.4), β -HCG: <0.2 IU/ml (0-10), AFP: 2.1 ng/ml (0-8.1), and urinary VMA: 2.5 mg/g creatinine (<18) were all in normal ranges. However, serum total testosterone: 457 ng/dl (<10), androstenedion: 3.35ng/ml (<0.5) and DHEA-SO4: 206 mcg/dl (<35) were measured higher than normal ranges.

Radiologic evaluation

Abdominal ultrasonography (USG) revealed right adrenal, 22x17 mm-sized mass. Scrotal ultrasound was normal. Magnetic resonance imaging (MRI) scanning revealed 16x14x17 mm mass which was isointense with muscle in T1 and hyperintense in T2 images. Abdominal CT showed a 16x11 mm nodular, hypodense mass with 35 Hounsfield Unite (HU).

Surgery, pathology and hormonal changes

The patient underwent adrenalectomy, and the mass was resected in one piece.

Histopathological examination revealed oncocytic variant ACC with 50 g weight (2 cm³).

Histologically, the surgical border of the tumour, which was limited to the adrenal gland and capsule of the adrenal gland was intact. The capsule inked was the surgical margin.

Neoplastic tissue had an expansile pattern. Normal adrenocortical cell component was seen in a few line and intermixed with neoplastic cells. Retroperitoneal lymph node involvement and vascular invasion were not seen. Immunohistochemical analysis revealed positive for MART 1, synaptophysin, inhibin, and negative for chromogranin, S100, EMA. Ki-67 proliferation index was 10%. Twenty mitoses were counted per 50 high power fields with the help of Phospho-Histone H3 (PHH3) (Figure 1). Total testosterone, androstenedione and DHEA-SO4

levels decreased to <10 ng/ml, <0.3 ng/ml and 102 mcg/dl at 12th hour, <10 ng/ml, <0.3 ng/ml and 57mcg/dl at 24th hour (Table 1).

Treatment

PET-CT and thoraco-abdominal CT were found normal as part of the staging workup. Staging of this oncocytic variant ACC according to Children's Oncology Group (COG) (7) classification was evaluated as Stage I. No further therapy was planned due to Group I (complete resection and tumor volume <200 cm³ and negative markers after surgery) according to TREP (Rare Tumors in Pediatric Age) (8). Any treatment was not applied to the patient. He was followed-up closely with physical examination and USG.

Evaluation after relapse

Three-month later from surgery, the child then presented with swelling of the left leg with a few weeks of history. Painless, immobile, rough 6x8 cm swelling between proximal anteroposterior femoral and the inguinal region was detected. MRI scanning revealed 9x4x3.5 cm mass which was isointense with muscle in T1, hyperintense in T2 images with dense contrast enhancement. The mass compressed to the superficial femoral vein and surrounded 200 degrees of the femoral artery.

The tru-cut biopsy was performed first. The pathology result was reported as compatible with metastasis of oncocytic variant ACC without immunohistochemistry. After extensive resection of the mass, histopathological examination revealed embryonal RMS, which was 8.5x5x4 cm sized, grey-white coloured, and solid (Figure 2). Histologically, the surgical border of the tumour, which was limited to muscle was intact with 5% focal necrosis. Lymphovascular invasion was not detected. Immunohistochemical analysis revealed positivity for desmin, Myo-D1, and muscle-specific-actin (MSA). MART 1, synaptophysin, S100, inhibin, chromogranin, CK7, CK20, MPO, and EMA were negative. Ki-67 proliferation index was 70% (Figure 2). We did not look for the ARMS translocations. PET-CT and thoraco-abdominal CT evaluation were found to be all normal as part of the staging workup. Nodal and pulmonary spreading was not detected. Extend of the RMS was defined according to the Intergroup RMS study (IRS) IV staging system. The patient was evaluated as pretreatment Stage III, postoperative Group I, and low subset B risk.

Genetic evaluation

A pedigree chart was made. No consanguinity was detected. Karyotype analysis of the patient was normal (46; XY). Testing for tumour protein (TP53) variant by DNA sequence analysis was positive in the peripheral blood sample, but FISH was negative.

Treatment

The patient was treated with chemotherapy consisting of vincristine, cyclophosphamide, and actinomycin-D according to the Protocol POG D-9602-VAC. Revision of pathological samples performed again. Sarcomatous component of oncocytic variant ACC was not found. The patient was evaluated at ten weeks from the beginning of the VAC regimen, and he was in remission both ACC and RMS sites. His disease was discussed with the radiotherapy department for local therapy of extremity RMS. Radiation oncology refused to give RT owing to remission of disease and age under 3 years. At 24th weeks of treatment, 2x2 cm sized, inguinal mass in left sartorius muscle which was enhanced after injection of contrast agent and compatible with lymphadenopathy was detected with MRI. The mass was excised, and the pathological result was compatible with RMD metastasis. The patient was evaluated as relapse and progression under chemotherapy treatment, and the treatment was changed with ICE (ifosfamide, carboplatin, etoposide) regimen. After three cycles, he was in remission. Radiotherapy was given for local control of RMS. After the 6th cycles of ICE, the patient was in good condition with no tumour recurrence, and treatment was stopped. However, he came back six months later with left leg pain due to mass and its press on the femoral artery and nerve. Thrombosis and Malign mesenchymal tumour protocol and sorafenib were started.

Surgeons recommended amputation due to nerve and lymphatic invasion of the tumour. However, the patient family refused the amputation. He died due to progressive disease 2, 5 years after diagnosis.

Discussion

Although most cases of malignancies appear to be sporadic, some syndromes which are associated with malignancy or malignancies in patients can be detected in oncology practice. Even if any association is not found, unusual associated malignancies can be evaluated for germline variants. In this study, we aim to describe an association of cancers with no family history in a child with oncocytic variant ACCs and RMS with the help of genetic evaluation. Li-Fraumeni syndrome (LFS), Beckwith-Wiedemann syndrome (BWS), multiple endocrine neoplasm type 1 (MEN-1) are at risk for developing certain types of cancers such as ACC, RMS (9). Especially, LFS, which is associated with a 40% risk of malignancy before the age of 16 years, high mortality rates, and second primary malignancies, is an autosomal disorder (10, 11). TP53 tumour suppressor gene on chromosome 17p13 in LFS, GNAS 1 variant, abnormalities of 11p15.5 in BWS and variants of the MEN-1 gene on chromosome 11q13 in MEN-1 may be detected in some patients with malignancy (12-15). Six per cent of patients with second malignancies and no familial features of LFS have a germline TP53 variant a sample of 59 patients (16). Germline TP53 variants with no familial features of LFS are identified in 50–80% of children with ACC and 10% with rhabdomyosarcoma (RMS) (17, 18). A variant related to malignancy may not be detected like our patients. In this study, an extensive pedigree was obtained. No family history of any other malignancies was documented in this family. Our patient did not have clinical features of BW and McCune-Albright syndrome. Thus, we decided to evaluate genetically because of sporadic malignancy. ACC is an extremely rare tumour. It accounts for 0.2% of childhood cancers (12). In our country, ACC accounts for 6.9 of carcinomas and other malignant epithelial tumours, and 0.19% of childhood cancer (3). Although most cases of ACCs appear to be sporadic, some have been described as a component of several hereditary cancer syndromes (9). Virilization can be seen owing to increased DHEA and DHEA-S production (13). In this case, DHEA-S, androstenedione, and testosterone were measured high with virilization. The absence of hormonal hyperactivity is associated with poor prognosis because of the advanced stage of the tumour at diagnosis (14). Hormonally active status of this case was very significant in early diagnosis. Also, there was clinical evidence of virilization. The levels of total testosterone, androstenedione, DHEA-SO₄ were highly elevated at the time of diagnosis. After surgery, the levels of these hormones decreased to an average level in the 24th hour. The survival rates of Stage I are higher than others (15). Our patient was followed-up without treatment after surgery. The primary site was normal in the follow-up.

Oncocytic variant ACC is a rare disease with low incidence. More than 80% are benign or with low malignant potential. It has been described in only 147 cases between 1986 and 2013 (4, 16, 17). Eighty per cent of them are detected incidentally owing to non-functional adrenal mass except 17% of them. (4) In addition to this, the sarcomatous component may be accompanied (1). Rhabdomyosarcoma as second cancer developed in the follow-up.

Rhabdomyosarcoma represents 6.5% of childhood cancers, and 52.9% of the soft tissue sarcomas (3). Somatic variants of the TP53 gene can be seen in as many as 50% of cases; however, germline variants are much less common and tend to be associated with a lower age (average age 22 months) at presentation (18, 19). Although this case was hormonally active, the sarcomatous component was not found.

There is no definitive pattern on CT scan or MRI. (4) On the CT Hounsfield Scale, adenoma/hyperplasia and carcinoma are assigned a value of 16.2 ± 13.6 and 36.9 ± 4.1 , respectively (20). Specificity and sensitivity of PET-CT are >95% (21). The mass was

compatible with non-adenoma owing to 35 HU. PET-CT was performed after surgery. Evaluation of disease with PET-CT was normal in staging workup.

Clinicopathological, oncocytic variant ACC differs from conventional ACC. There is no preference for males or females. It is smaller and lighter than conventional ACC with left predilection. The oncocytic variant has rare mitoses including no atypia, low rate of necrosis, fibrosis, and venous, sinusoidal, and capsular invasion (22). These features were mostly compatible with our case's pathology and clinical features except the high mitotic rate and involvement of the right side.

Proposed major [a mitotic rate of more than five mitoses per 50 high power fields, any atypical mitoses or venous invasion] and minor [large size (110 cm and 1200 g), necrosis, capsular invasion or sinusoidal invasion] criteria in distinguishing malignant tumours have been analyzed by Bisceglia et al. (23). Defining criteria (predominantly cells with eosinophilic and granular cytoplasm, a high nuclear grade, and a diffuse architectural pattern) for oncocytic tumours have been outlined. The presence of 1 major criterion indicating malignancy, 1–4 minor criteria indicating uncertain malignant potential (borderline) and the absence of all major and minor criteria indicative of benign mass. Mitotic rate was more than five mitoses per 50 high power fields. When mitosis was evaluated with phospho-Histone H3 (PHH3), 20 mitoses were counted per 50 high power fields. Venous, capsular, sinusoidal invasions, necrosis were not detected. It met all defining criteria. The mass <100 g is compatible with a good prognosis (24). Our patient was evaluated as Stage I because of his adrenal mass under <100 g (the patient's mass ≈50 g) with total excision. However, it was assessed as a malign mass owing to 1 major criterion (high mitotic rate).

The molecular pathogenesis of sporadic ACCs is less well understood. Activation of proto-oncogenes and oncogenes on chromosome 4, 5, and 12, and inactivation of tumour suppressor genes on chromosome arms 1p and 17p may be related to progression from adenoma to carcinoma (25). Loss of heterozygosity at 17p13 is common, but only about one-third of these tumours have a variant of TP53. TP53 might not be the only or major tumour suppressor gene at 17p related to ACCs. Another suppressor gene which is yet unidentified can be present and effective in this locus (26). ACCs are associated with multiple somatic gene alterations. It is difficult to identify the exact genetic changes (27). Amplification of the steroidogenic factor 1 (SF-1) gene as well as germline TP53 variant in Southern Brazil, loss of heterozygosity (LOH) of 11p15 with overexpression of insulin-like growth factor (IGF)-II as well as other growth-related tumour suppressor genes at this locus may explain this (28, 29). We only studied TP53 analysis owing to financial problems. This status is our limitation. However, the TP53 variant was positive in sequence analysis of gen.

Use of radiation ionizing images as PET and CT scan for the follow-up of this small child at risk of other malignancies. Because of this, we used MRI and abdominal USG only to avoid repeated irradiation after the second malignancy. External radiotherapy to the leg after 10-week from the beginning of chemotherapy was not given by the radiotherapy department owing to remission of the disease. However, we had to plan to provide radiotherapy after the recurrence of the disease for local control.

The occurrence of ACC as a part of a syndrome is clinically significant because of the choice of treatment, caution with radiation therapy in patients with LFS, individualized screening for other cancers in these syndromes with mammography, colonoscopy, and identification family members at risk (30).

In conclusion, a multidisciplinary team approach, including oncology, surgery, endocrinology, pathology, radiation oncology, and genetic counselling is necessary. The Cost-effectiveness of cancer screening with colonoscopy is not considered controversial for well-defined cancers such as colon cancer, but no data are available for ACCs. Genetic evaluation should be suggested for patients with second cancer. This patient has a TP53 variant. Variants

can inactivate TP53 in about half of all human cancers. Unusual association of malignancies with the absence of a positive family history of malignancies strongly suggests a problem in tumour suppressor genes or new variants. Whole genomes analyses will give us important information on the development of ACCs and secondary cancer.

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Fig. 1. a. Enlargement of phallus, stage II pubic hair development. b. Abdominal CT showing right adrenocortical carcinoma. c. The mass after adrenalectomy. d. Oncocytic adrenocortical carcinoma, oxyphilic cell population, Hematoxylin-eosin (H-E), immunohistochemical expression, (magnification x200). e. Oncocytic adrenocortical carcinoma, Melan-A (MART-1) immunohistochemical expression, (magnification x200).

Uncorrected proof

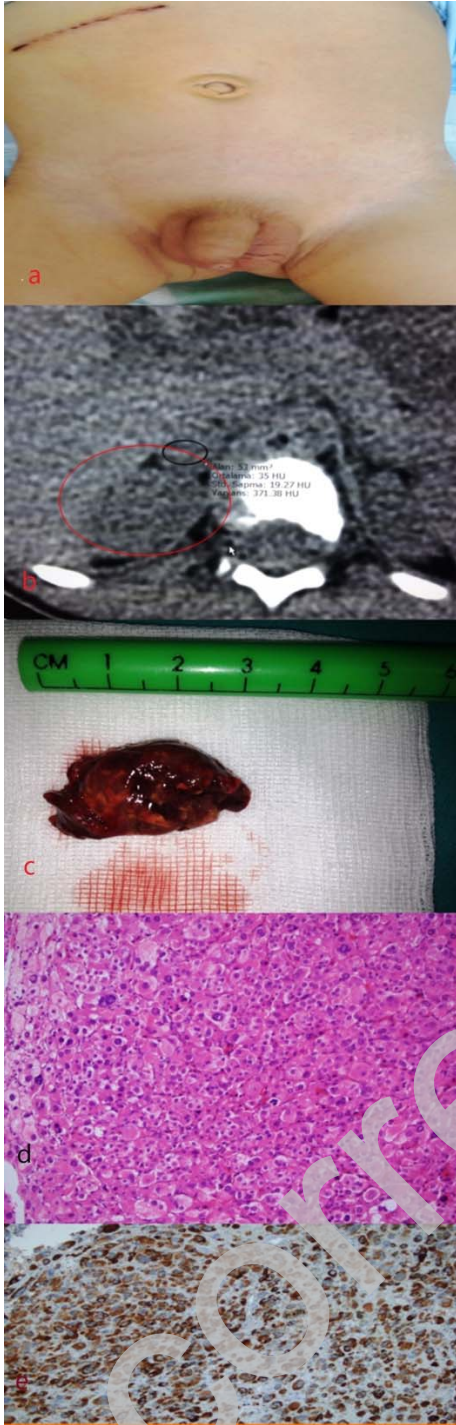


Fig. 2. a. Femoral MRI showing left side rhabdomyosarcoma. b. X-ray graphy showing left femoral mass. c. Rhabdomyosarcoma, HE, (magnification x400). d. Rhabdomyosarcoma, Desmin positivity, (magnification x200).

